Roy J. Britten, 1919–2012: Our early years at Caltech

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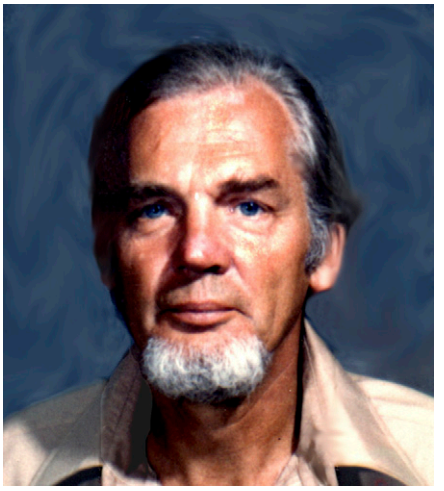
Roy Britten died in Costa Mesa, California on January 21, 2012, of pancreatic cancer at age 92. His work in the 1960s, in which he used renaturation kinetics to provide a quantitative image of the single-copy and repetitive sequence content of animal genomes, was of gigantic intellectual import, and it essentially built the ground floor of the edifice that we call genomics today. He was elected a member of the National Academy of Sciences in 1972. At the beginning of the 1970s, Roy and I teamed up as scientific partners, and we relocated to Caltech. At Caltech, we worked together for over one-quarter of a century, and most of the following work consists of a very brief retrospective on the eventful first decade of our Caltech partnership. Later, in the 1990s, Roy returned to focus on his old interests in evolutionary processes that affect genomic sequence content. He continued to carry out computational analyses on the roles of mobile elements and other processes that ceaselessly remodel genomes, particularly primate genomes, almost until his death; his last paper, "Transposable element insertions have strongly affected human evolution," was published in PNAS in November of 2010 when he was 91 years old.

Roy was born in Washington, DC, to accomplished parents, both of whom held intellectual jobs in Washington agencies: Rollo was a statistician at the National Bureau of Standards, and Mimi worked at the National Research Council. Roy grew up in Alexandria, Virginia, and in 1940, he went to Princeton to study physics. The war interrupted, and Roy, who ultimately was a confirmed pacifist, joined a Manhattan Project effort, which as he often stated, was "fortunately" a complete failure. After this work, he continued at Princeton, now in graduate school, and he took his PhD in 1951 working on astigmatic mirrors for focusing cyclotron beams. Roy immediately switched to biophysics, however, and he became a junior member of the biophysics group at the Department of Terrestrial Magnetism (DTM) of the Carnegie Institution of Washington. He remained there for the next 20 years, and he discovered the nature of the animal genome as well as contributed novel and incisive quantitative methodologies for study of transcriptional processes.

My later partnership with Roy began as a "train collaboration" in early 1967, when



Roy J. Britten.

I discovered the work of Roy's group in the Annual Report of the Director of DTM. This work was an instant eye opener for me, because it was immediately apparent that Roy's discoveries of how to isolate single-copy DNA by hydroxyapatite chromatography and how its renaturation could be controlled according to rationally computed kinetic parameters opened the way to measurement of the complexity of gene expression in early development. This interest was my abiding, but theretofore frustrated, interest. I was then in New York as a junior faculty member at Rockefeller Institute, and I took the train down to Washington, DC, to visit Roy at DTM, which on first encounter, seemed to be a remote, rarified, almost celestial temple of quantitative science. Roy and I seemed to have stimulated each other's minds, and the rest is history; 2 years later, we published our 1969 work, "Gene regulation for higher cells: A theory." This model was a hierarchical network model for developmental gene regulation replete with signal inputs, pleiotropic regulatory functions, etc., and many of its essential predicted logic features can be seen currently in experimentally solved developmental gene regulatory networks. The experience of working intensely on that model made us decide that we should cast in our lot together, and the opportunity soon arose at Caltech, where we opened shop in 1971. Roy was at Caltech's Kerckhoff Marine Lab (KML), and I was on the main campus in Pasadena, which were about a 1-hour drive apart. Roy was a great blue water sailor as had been his parents, and for some years, he lived with Barbara, his wife from Princeton days, and their two sons, Ken and Gregory, on a large and beautiful schooner called Tiercel, which was moored in Newport Bay, very close to KML.

One of the first things that we did was construct a (then) large joint grant application, which in modern terms, would have to be described as a genome-oriented systems developmental biology project (we just referred to it as "The Macroproject"). This grant marked the initiation of our choice of the sea urchin embryo as our model developmental system, a decision that stuck for the next 40 years until this day. I shall always remember how we wrote that grant. Together with Jane Rigg, my laboratory administrator and companion, Roy, and Barbara (and I do not remember who else), we piled into Tiercel; Roy rigged the schooner, and we sailed in a nice breeze down the coast to the next harbor going south, Dana Point. There, we anchored for several days and wrote the grant on board. Despite this (or perhaps because of it), amazingly, The Macroproject was funded by the National Institute of Child Health and Human Development, and we were in business.

In that first decade, our physical–chemical focus on DNA and embryo RNAs seemed to generate new discoveries explosively. We quickly became interested in how repetitive DNA sequences are distributed in the genome, and we devised a way to find out their average disposition. DNA was sheared to various lengths and renatured just to the point where most repetitive sequence would be found in duplex form and the complexes bound to hydroxyapatite, which at certain salt concentrations, traps only dsDNA. As length increases, the single-stranded tails representing single-copy sequences adjacent to the duplexed repeats would be trapped as well until the length approximates the distance where another repetitive sequence would occur. By fitting data measuring the amount of DNA bound as a function of fragment length to a simple mathematical model, we quickly discovered that sea urchin, mammalian, and *Xenopus* DNAs all contained large fractions of sequence in which repetitive sequences only a few hundred base pairs in length are interspersed with single-copy

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sequences a few kilobases long. We found that the repetitive sequences of these genomes consist of complex assemblages of diverse repeat families of different sizes and different degrees of intrafamiliar similarity and that even closely related species (members of the same genus) have very different numbers of genomic repeats of given families. At the time, surprisingly, we also found that most primary RNA transcripts display the same interspersed repetitive sequence structure, and because the repeats are oriented randomly with respect to strand, these RNAs would readily renature partially as well, forming H structures that could be visualized in the electron microscope. We devoted an enormous amount of effort to measuring the complexity of the polysomal mRNAs of sea urchin embryos of various stages, and thus, we discovered that many thousands of genes are expressed in early development, most at a very modest level and a few percent more highly. In addition, we developed methods to measure the absolute synthesis and turnover rates of populations of embryo mRNA and nuclear RNA, and we, thus, established the real-time dynamics of embryo gene expression. Roy had a physically large computer that filled up a small room next to his office at KML, and all these measurements on DNAs and RNAs eventually turned into least squares fits churned out on reams of computer paper. In the 1980s, a friend of mine, who was a well-known *Drosophila* developmental geneticist, once said that the type of knowledge that we were generating was "everything you don't want to know about development," but a couple of decades on, with the advent of modern molecular biology methods and genomics and the current focus on system-level processes, much of it turned out to provide an invaluable platform for prediction, experiment, and interpretation.

Two interesting episodes hung on our investigations of genomic sequence organization in the early 1970s. At that time, I was Director of the MBL Embryology Course; one summer, Roy and I took our hydroxyapatite columns to Woods Hole, and we entrained the whole class into examining sequence organization in every marine creature that we could get DNA out of from jellyfish to oysters and horseshoe crabs. We discovered that genomic sequence organization is amazingly variable: some genomes seemed to contain relatively huge amounts of repetitive sequence, others lacked almost any short interspersed repeat sequences, which was found in *Drosophila*, and other genomes were organized, like human, sea urchin, and *Xenopus* DNA. These differences are the rapidly evolving legacies of distinct histories of genomic mobile element infestation, and as quickly became apparent, gross sequence organization evidently had nothing to do with long-distance phylogenetic relations. Also at this period, we got into a major scientific argument with people who had a diametrically opposed image of how animal genomes are organized; this school was led by the late Charles A. Thomas (Charlie), who believed that the genome consisted of tandem repetitive sequence. This theory required rejection of all of Roy's 1960s renaturation results as well as our more recent sequence organization studies, and it was published in multiple back to back papers by Charlie and his associates in the same issue of *Journal of Molecular Biology* that carried our first report of repetitive/single-copy sequence interspersion. Charlie gave these papers the Wagnerian title "The Ring Theory." A few years later, the tandem repeat model dissolved away, but for a time, Roy and I had a very lively series of debates with Charlie on stages at meetings from Australia to Caltech. The end result was that Charlie became a close friend, and everyone in the field finally agreed on how Roy had shown animal genomes to be organized.

Roy Britten's schooner, the Tiercel, in Newport Bay. Photo by Robert C. Angerer.

Roy passed away at a time when the mantras of systems biology are gathering ever more force. Leaving aside the aspects of this new umbrella that have little to do with causal experimental analysis of biological process, it can truly be said that one of Roy's most important legacies was to show a style of measurement and problem solving that addresses processes directly at the system level. In the domain of the most important biological molecules, DNA and RNA, Roy was the founding systems biologist.